

## Reduction in non syndromic oral clefts following mandatory flour fortification with folic acid in Northern Iran

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Received: 10 May 2013

Accepted: 28 Sep 2013

Published: 7 May 2014

### Abstract

**Background:** Several studies have examined the effects of folic acid fortification on the occurrence of orofacial clefts. This study was carried out to evaluate the impact of flour fortification with folic acid on oral clefts in Northern Iran.

**Methods:** In this hospital based study from March 2006 to September 2009, we screened the total number of live births at all hospitals in Golestan province in North of Iran, as well as the number of pregnancies affected by non syndromic oral clefts, per 100000 births during the periods before (March 2006 –June 2007), during (July 2007-March 2008) and after (May 2008- September 2009) folic acid fortification of flour was implemented. Non syndromic Oral clefts were defined in accordance with the International Classification of Diseases, 10th revision (ICD-10).

**Results:** The prevalence of oral clefting reduced from 64.2 per 100000 births before fortification to 32.2 per 100000 after flour fortification with folic acid. The preventive fraction rate of oral clefting after fortification period in comparison with before period was 49.8% (OR=0.502 95% CI 0.26-0.97, p=0.036).

**Conclusion:** This study showed that flour fortification with folic acid is associated with a significant reduction in the rate of oral clefting in Golestan province in Northern Iran.

**Keywords:** Oral clefts, Folic acid, Flour, Fortification, Iran.

*Cite this article as:* Golalipour M.J, Vakili M.A, Kaviani N. Reduction in non syndromic oral clefts following mandatory flour fortification with folic acid in Northern Iran. *Med J Islam Repub Iran* 2014 (7 May). Vol. 28:29.

### Introduction

Cleft lip with or without cleft palate is one of the most common congenital anomalies of multi factorial etiology (1-3).

The oral clefting rate varies from one of every 500 to 2,000 births in different parts of the world (4). The prevalence of oral clefting was reported 0.97 per 1000(1 in 1025) birth in a hospital based study in north of Iran during 1998-2003 period (5).

Several factors including gender, race/ ethnicity, geographic location, nationality, socioeconomic status, nutritional and periconceptional consumption of folic acid affect on prevalence rate of oral clefts (4-20).

Researches have shown that periconceptional folic acid consumption can reduce the occurrence of cleft lip with or without cleft palate and cleft palate alone (7-12, 21-24).

In spite of usefulness of periconceptional folic acid consumption to reduce oral clefts, many childbearing age women do not consume periconceptional folic acid. The Studies reported that less than 45% of pregnant women have consumed folic acid before conception (25, 26).

Several studies have examined the effects of folic acid fortification on the occurrence of orofacial clefts (27-33).

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Considering the evidence on the role of folic acid to reduce the occurrence of Neural Tube Defects (NTDs) and also available experiences on fortification with folic acid and Based on the World Health Organization recommendations, through a national law, named Mandatory wheat flour fortification with folic acid (1.5 ppm: 150 Micro gram per 100 g flour.) was implemented in Golestan province in North of Iran since March 2006. Regarding to lack of studies on the efficacy of folic acid fortification on oral clefts in Iran, this study was done to evaluate the impact of flour fortification with folic acid on oral clefts in North of Iran.

### Methods

This Population surveillance hospital-based study was performed in sixteen hospitals in Golestan province in Northern Iran. Regarding to wheat flour fortification in bread industries and bakers according to national law, all people consume of fortified flour in Golestan province. Therefore 100% of population in this province has used fortified wheat flour since 2007.

Ethical approval for the study was obtained from the ethics committee of Golestan University of Medical Sciences.

All live births (104232) were included in the study who was admitted in hospitals from March 2006 to September 2009. Golestan Province located in Northern Iran. This Province has a population of about 1.8 million and covers an area of about 20,460 square kilometers with an annual rate of more than 31000 annual deliveries. In each hospital, two members of the staff (registered nurse) have been recruited and trained to revise all births, to register and to describe non syndromic oral clefts. Types of Oral clefts registered were cleft lip, cleft palate, and cleft lip with cleft palate according to the International Classification of Diseases (ICD10). Oral clefts were approved by a pediatrician. Syndromic oral clefts were excluded from the study. The total number of births at all hospitals in Golestan province, as well as the number of

pregnancies affected by oral clefting during the periods before (March 2006 –June 2007), during (July2007-March 2008) and after (May 2008- September 2009) folic acid fortification of flour were screened. Rate of oral clefts was defined as the number of oral clefts cases, divided by the total number of births.

### Statistical Analysis

The prevalence rate per 100000 was estimated to evaluate the effect of flour fortification in three time intervals (before, introduction after fortification). For comparing prevalence rate between each of two times, we used preventive fraction (1-OR), Odds Ratio (OR) and confidence interval (CI) for OR. Furthermore, collected data were analyzed by SPSS version 15.0 and rates were compared with the chi-square test. P-value of 0.05 or less was considered statistically significant.

### Results

Between 2006 and 2009, fifty one non syndromic oral clefting cases were recorded, of which 30 (58.8%) were males and 21 (41.2%) were females. Cleft lip with palate was the most common type of anomaly (37.3%), followed by cleft lip (33.3%) and cleft palate (29.4%).

In the period before flour fortification with folic acid, prevalence rate of oral clefts was 64.2 per 100000 live births, whereas in introduction period of fortification the prevalence was 59.8, and in the period after fortification it was 32.2 per 100000 live births.

The preventive fraction rate of oral clefting in introduction period in comparison with before fortification period was 7% [OR=0.932, 95% CI 0.48-1.82, p=0.83] (Table 1).

Also, the preventive fraction rate of oral clefting after fortification period in comparison with introduction period was 46% [OR=0.54, 95% CI 0.26 -1.12, p=0.09] (Table 2).

Table 1. Comparison of pre-fortification and introduction period of oral clefts per 100,000 live births; North Iran, 2006–2009

Period	Years	Live Birth	Oral Clefts (No)	Rate per 100000	OR(Odd Ratio)	95% CI
Before Fortification	March 2006 –June 2007	34295	22	64.2		
Introduction Period	July 2007- March 2008	23409	14	59.8	0.932	0.48 – 1.82

Table 2. Comparison of pre-fortification, introduction period and post-fortification of oral clefts per 100,000 live births; North Iran, 2006–2009

Period	Years	Live Birth	Oral clefts(No)	Rate per 100000	OR(Odd Ratio)	95% CI
Introduction Period	July2007-March 2008	23409	14	59.8		
After Fortification Period	May 2008- September 2009	46528	15	32.2	0.54	0.26-1.12

Table 3. Comparison of pre-fortification and post-fortification of oral clefts per 100,000 live births; North Iran, 2006–2009

Period	Years	Live Birth	Oral clefts(No)	Rate per 100000	OR(Odd Ratio)	95% CI
Before Fortification	March 2006 – June 2007	34295	22	64.2		
After Fortification	May 2008- September 2009	46528	15	32.2	0.502	0.26-0.97

Indeed, the preventive fraction rate of oral clefting after fortification period in comparison with before fortification period was 49.8% [OR=0.502, 95% CI 0.26 -0.97, p=0.036] (Table 3).

## Discussion

This study has demonstrated that flour fortification with folic acid is associated with a reduction in rates of oral clefting in the North of Iran. Our study showed significant reduction in the prevalence rate of oral clefting after flour fortification with folic acid in comparison with pre-fortification period. Therefore, we suggest that difference of oral clefting rate between pre and post fortification period related to flour fortification with folic acid.

Several studies have reported non-significant reduction in the prevalence rate of oral clefting after fortified their food supplies with folic acid.

Hashmi et al study (2005) in Texas, USA reported non-significant reduction in CL/ P prevalence by 3% (32). Also, Canfield et al (2005) from the National Birth Defects Prevention Network using data from multiple state registries found a 5% decline in

cleft lip with or without cleft palate post-fortification (29). Indeed, Simmons et al (2004) reported non-significant reduction (14%) in prevalence of oral clefts in Arkansas between the pre (1996-1998) and post-fortification (1999-2000) periods (28). Castilla et al study (2003) in an evaluation of the effects of fortifying wheat flour with folic acid in Chile reported no significant changes in prevalence of oral clefts (33). Furthermore, Ray et al (2003) assessed the occurrence of orofacial clefts in Ontario, Canada among women who had undergone a maternal serum screening following folic acid fortification of grains and reported a non-significant increase in the prevalence of oral clefts after 2 years of fortification of cereal grain products between 1998 and 2000(27).

On the other hand, few studies reported significant reduction of oral cleft after fortification with folic acid. Canfield et al (2005) from the National Birth Defects Prevention Network using data from multiple state registries found a significant decline (12%) in cleft palate alone(29). Yazdy study (30) with analysis of the data from birth certificates suggested that folic acid

fortification in the United States is associated with a significant decline (6%) in the prevalence of orofacial clefts. She reported the rate of Orofacial clefts were 85.2 per 100,000 births during the period before folic acid fortification (1990–1996) and this prevalence dropped to 80.2 per 100,000 births after folic acid fortification became mandatory (October 1998–December 2002) in the United States (PR  $\frac{1}{4}$  0.94; 95% CI: 0.92–0.96). According to Yazdy report, only non-Hispanic White mothers had a statistically significant decline in cleft prevalence following folic acid fortification (30).

Indeed, Johnson and Little (2008) in a meta-analysis of fortification studies in the United States and Canada have shown a reduction of approximately 7% and 8% in the prevalence rate of Cleft lip with or without cleft palate and cleft palate alone, respectively (34). The differences in findings of various studies can be related to nutritional habits, duration of study, data sampling and health service care.

Our results indicated that flour fortification in this area has resulted in a significant reduction in the prevalence rate of non syndromic oral clefting among live births in North of Iran, because the bread which provided from flour is the main food in this area. Another study has indicated that the current periconceptional administration of folic acid intake in women with childbearing age is low (35).

Of course, other factors including periconceptional administration of folate and nutritional factors which is handled by health service in Golestan province may be effective on reduction of oral clefts. According to our results, we recommend this program could be implemented in addition to the consumption of periconceptional folic acid supplements in order to reduce birth defects.

### Conclusion

This study showed that flour fortification with folic acid is associated with a significant reduction in the rate of oral clefting in Golestan province in Northern Iran.

### Acknowledgements

The authors thank to the director and personnel of gynecology and pediatrics ward of all hospitals in Golestan province and also Miss Maliheh Sedehi, our colleague in the Gorgan Congenital Malformations Research Center. This study was supported (Grant number: 35/2376) by the Gorgan Congenital Malformations Research Center and the Research Deputy of Golestan University of Medical Sciences, Gorgan, Iran.

### References

1. Abramowicz S, Cooper ME, Bardi K, Weyantr J, Marazita ML. Demographic and prenatal factors of patients with cleft lip and cleft palate: A pilot study. *J Am Dent Assoc.* 2003 Oct; 134(10):1371-6.
2. Tolarová MM, Cervenka J. Classification and birth prevalence of orofacial clefts. *Am J Med Genet.* 1998 Jan 13; 75(2):126-37.
3. Wehby GL, Murray JC. Folic acid and orofacial clefts: a review of the evidence. *Oral Diseases.* 2010 January; 16(1): 11–19.
4. Marazita ML. Genetic etiologies of facial clefting. In: Mooney MP, Siegel MI, eds. *Understanding craniofacial anomalies: The etiopathogenesis of craniosynostosis and facial clefting.* New York: Wiley. 2002:147-162.
5. Golalipour MJ, Mirfazeli A, Behnampour N. Birth prevalence of oral clefting in northern Iran. *Cleft Palate Craniofac J.* 2007 Jul; 44(4):378-80.
6. Vanderas AP. Incidence of cleft lip, cleft palate, and cleft lip and palate among races: a review. *Cleft Palate J.* 1987 Jul; 24(3):216-25.
7. Czeizel AE, Toth M, Rockenbauer M. Population-based case control study of folic acid supplementation during pregnancy. *Teratology.* 1996 Jun; 53(6):345-51.
8. Itikala PR, Watkins ML, Mulinare J, Moore CA, Liu Y. Maternal multivitamin use and orofacial clefts in offspring. *Teratology.* 2001 Feb; 63(2):79-86.
9. van Rooij IA, Ocké MC, Straatman H, Zielhuis GA, Merkus HM, Steegers-Theunissen RP. Periconceptional folate intake by supplement and food reduces the risk of nonsyndromic cleft lip with or without cleft palate. *Prev Med.* 2004 Oct; 39(4): 689-94.
10. Shaw GM, Lammer EJ, Wasserman CR, O'Malley CD, Tolarova MM. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. *Lancet.* 1995 Aug 12; 346(8972):393-6.
11. Clark JD, Mossey PA, Sharp L, Little J. Socioeconomic status and orofacial clefts in Scotland, 1989 to 1998. *Cleft Palate Craniofac J.* 2003 Sep;

40(5):481-5.

12. Bailey LB, Berry RJ. Folic acid supplementation and the occurrence of congenital heart defects, orofacial clefts, multiple births, and miscarriage. *Am J Clin Nutr*. 2005 May; 81(5):1213S-1217S.

13. Das S.K, Runnels RS, Smith JC, Cohly HHP. Epidemiology of cleft lip and cleft palate in Mississippi. *South Med J*. 1995 Apr; 88(4):437-42.

14. Manyama M, Rolian C, Gilyoma J, Magori C C, Mjema K, Mazyala E, et al. An assessment of Orofacial clefts in Tanzania. *BMC Oral Health*. 2011 Feb 2; 11:5. doi: 10.1186/1472-6831-11-5.

15. Wang W, Guan P, Xu W, Zhou B. Risk factors for oral clefts: a population-based case-control study in Shenyang, China. *Paediatr Perinat Epidemiol*. 2009 Jul; 23(4):310-20.

16. Kim S, Kim WJ, Oh C, Kim JC. Cleft lip and Palate Incidence among the live births in the Republic of Korea. *J Korean Med Sci*. 2002 Feb; 17(1):49-52.

17. Elahi M M, Jackson I T, Elahi O, Khan A H, Mubarak F, Tariq G B, et al. Epidemiology of Cleft Lip and Cleft Palate in Pakistan. *Plast Reconstr Surg*. 2004 May; 113(6):1548-55.

18. Smit R, Fowler PV. Non-syndromal orofacial clefts in the Canterbury/West Coast region during the 2000-2009. *N Z Dent J*. 2010 Dec; 106(4):129-31.

19. Murray JC, Daack-Hirsch S, Buetow KH. Clinical and epidemiologic studies of cleft lip and palate in the Philippines. *Cleft Palate Craniofac J*. 1997 Jan; 34(1):7-10.

20. Durning P, Chestnutt IG, Morgan MZ, Lester NJ. The relationship between orofacial clefts and material deprivation in wales. *Cleft Palate Craniofac J*. 2007 Mar; 44(2):203-7.

21. Tolarova M, Harris J. Reduced recurrence of orofacial clefts after periconceptional supplementation with high-dose folic acid and multivitamins. *Teratology*. 1995 Feb; 51(2):71-8.

22. Loffredo LC, Souza JM, Freitas JA, Mossey PA. Oral clefts and vitamin supplementation. *Cleft Palate Craniofac J*. 2001 Jan; 38(1):76-83.

23. Czeizel AE, Dobo M, Vargha P. Hungarian cohort-controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital abnormalities. *Birth Defects Res A Clin Mol Teratol*. 2004 Nov; 70(11):853-61.

24. Wilcox AJ, Lie RT, Solvoll K, Taylor J, McConaughy DR, Abyholm F, Vindenes H, Vollset SE, Drevon CA. Folic acid supplements and risk

of facial clefts: national population based case-control study. *BMJ*. 2007; 334(7591):464.

25. Sharpe G, Young G. Most pregnant women do not take folic acid. *BMJ*. 1995 Jul 22; 311(6999):256.

26. Wild J, Sutcliffe M, Scrorah CJ, Levere MI. Prevention of neural tube defects. *Lancet*. 1997 Jul 5; 350(9070):30-31.

27. Ray JG, Meier C, Vermeulen MJ, Wyatt PR, Cole DE. Association between folic acid food fortification and congenital orofacial clefts. *J Pediatr*. 2003 Dec; 143(6):805-7.

28. Simmons CJ, Mosley BS, Fulton-Bond CA, Hobbs CA. Birth defects in Arkansas: Is folic acid fortification making a difference? *Birth defect Res*. 2004 Sep; 70(9):559-64.

29. Canfield MA, Collins JS, Botto LD, Williams LJ, Mai CT, Kirby RS, et al. Changes in the birth prevalence of selected birth defects after grain fortification with folic acid in the United States: Findings from a multi-state population-based study. *Birth defect Res Clin mol Teratol*. 2005 Oct; 73(10):679-89.

30. Yazdy M M, Honein M A, Xing J. Reduction in Orofacial Clefts Following Folic Acid Fortification of the U.S. Grain Supply. *Birth Defects Research (Part A)*. 2007; 79(1):16-23.

31. Godwin KA, Sibbald B, Bedard T, Kuzeljevic B, Lowry RB, Arbour L. Changes in frequencies of select congenital anomalies since the onset of folic acid fortification in a Canadian birth defect registry. *Can J Public Health*. 2008 Jul-Aug; 99(4):271-5.

32. Hashmi SS, Waller DK, Langlois P, Canfield M, Hecht JT. Prevalence of nonsyndromic oral clefts in Texas:1995-1999. *Am J Med Genet A*. 2005 May 1; 134(4):368-72.

33. Castilla EE, Orioli IM, Lopez-Camelo JS, Dutra Mda G, Nazer-Herrera J. Latin American Collaborative Study of Congenital Malformations (ECLAMC). Preliminary data on changes in neural tube defect prevalence rates after folic acid fortification in South America. *Am J Med Genet A*. 2003 Dec 1; 123A(2):123-8.

34. Johnson CY, Little J. Folate intake, markers of folate status and oral clefts: is the evidence converging? *Int J Epidemiol*. 2008 Oct; 37(5):1041-58.

35. Abdollahi Z, Elmadfa I, Djazayeri A, Golalipour MJ, Sadighi J, Salehi F, et al. Efficacy of Flour Fortification with Folic Acid in Women of Childbearing Age in Iran. *Ann Nutr Metab*. 2011; 58(3):188-96.